General considerations:

- The purpose of this educational material is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians.

- The content of this educational material does not intend to replace the clinical criteria of the physician.

- If there is any correction or suggestion to improve the quality of this educational material, it should be done directly to the author by e-mail.

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PEARLS IN ALLERGY AND IMMUNOLOGY  July 2014

July 2014 – content:

• ALLERGIC RHINITIS IS A RISK FACTOR FOR TRAFFIC SAFETY (Vuurman EFPM, Vuurman LL, Lutgens I, Kremer B. Allergy 2014; 69: 906–912).


• REFRACTORY ASTHMA: MECHANISMS, TARGETS, AND THERAPY (Trevor JL, Deshane JS. Allergy 2014; 69: 817–827).


• A CASE OF TRANSIENT ACQUIRED C1 INHIBITOR DEFICIENCY (Melamed J, Ahuja-Malik A. Ann Allergy Asthma Immunol 2014; 113: 116-117).

• ALLERGIC CONTACT DERMATITIS (Fonacier LS, Sher JM. Ann Allergy Asthma Immunol 2014; 113: 9-12).

• CHANGING ROLES OF EOSINOPHILS IN HEALTH AND DISEASE (Furuta GT, Atkins FD, Lee NA, Lee JJ. Ann Allergy Asthma Immunol 2014; 113: 3-8).


• THE DRY NEEDLE TECHNIQUE (Coop CA, Yip SK, Tankersley MS. Ann Allergy Asthma Immunol 2014; 113: 120-121).


ALLERGY:

- **ALLERGIC RHINITIS IS A RISK FACTOR FOR TRAFFIC SAFETY** (Vuurman EFPM, Vuurman LL, Lutgens I, Kremer B. Allergy 2014; 69: 906–912):
  - Allergic rhinitis (AR): (i) definition: IgE-mediated inflammation of the nasal mucosa; (ii) prevalence: up to 40% of the population; (iii) impact: ↓ physical, psychological and social well-being, ↓ work and school performance, ↓ QoL, ↑ costs, ↑ risk of asthma and other comorbidities/complications; (iv) clinical manifestations: rhinorrhea, nasal blockage (most common and bothersome symptom), sneezing, itching, mouth breathing, snoring, nasal voice, cough, ‘allergic shiners’ (darkened lower eyelids due to chronic congestion), minor epistaxis; (v) comorbidities/complications: conjunctivitis, sinusitis, hyposmia, Eustachian tube dysfunction, middle ear effusion, otitis, ↓ hearing, lymphoid hypertrophy (adenoids, tonsils), pharyngitis, asthma, dental malocclusion, atopic eczema, pollen-food syndrome, sleep disordered breathing (snoring, microarousals, obstructive sleep apnea/hypopnea, chronic nonrestorative sleep), daytime sleepiness, ↓ cognitive functions, ↓ psychomotor functions, difficulty concentrating, fatigue, stress, impaired school or work performance, systemic inflammation; (vi) diagnosis: clinical history, anterior rhinoscopy, allergy testing (25% of AR cases are ‘local’ [entopy], which means that specific IgE is not detected by skin or serum tests); (vii) treatment: (depends on severity): allergen avoidance, antihistamines (oral, intranasal), corticosteroids (intranasal, oral), antileukotrienes, decongestants (oral, topical), allergen immunotherapy.

- **Mechanisms of sleep impairment in AR:** (i) breathing obstruction (microarousals, apneic episodes); (ii) ↑ inflammatory cytokines (e.g. IL-1β, IL-4, IL-6, IL-10, TNF-α, histamine); (iii) ↓ REM sleep (important restorative function); (iv) autonomic disturbance (cholinergic, adrenergic); (v) use of sedating antihistamines (histamine is important in the CNS to maintain arousal).

- Authors performed a double-blind randomized four-leg cross-over trial in 19 adults to evaluate the impact of AR symptoms (after an intranasal pollen challenge) on a driving test → (i) AR symptoms reduced driving performance (comparable to that seen at a blood alcohol level of 0.05%, the legal limit in many countries); (ii) treatment of AR (oral cetirizine or intranasal fluticasone furoate) partially counteracted its detrimental effect on driving.

- **Author’s commentaries:** (i) untreated AR can ↓ driving ability and ↑ patient’s risk; (ii) drug therapy can ↓ this impairment.

  - Atopic dermatitis (AD): (i) common chronic skin disease (3% of adults, 20% of children); (ii) prevalence has ↑ globally; (iii) impact: ↓ QoL, high costs, ↑ predisposition to skin infections and other allergies; (iv) multiple pathogenic factors: genetic, epigenetic, environmental; (v) clinical features: eczema, dry skin, pruritus, predisposition to skin bacterial, fungal and viral infections; (vi) immune abnormalities: defective epithelial barrier, defective innate immune responses, eosinophilia, ↑ IgE, ↑ TH2 and TH22 responses in the skin.

- **DOCK8 (dedicator of cytokinesis 8) deficiency:** (i) autosomal recessive hyper-IgE syndrome (HIES) with features of combined immunodeficiency; (ii) clinical features: severe viral infections
(especially by HSV, VZV, HPV, molluscum contagiosum virus and JC viruses), fungal and bacterial infections, severe allergies, cancer susceptibility (e.g. squamous cell carcinoma, lymphoma); (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ DC migration, ↓ production of antiviral cytokines, impaired TLR/MyD88 pathway, lymphopenia, ↓ T-cell chemotaxis, ↓ T-cell activation, ↓ T-cell survival, ↓ T-cell and B-cell memory, ↓ CD8+ T-cell and NK-cell cytotoxicity, ↓ germinal center formation, ↓ germinal center B cells, ↓ antibody production, impaired lymphoproliferation to antigens; (iv) only curative treatment: HSCT.

• **STAT3** (signal transducer and activator of transcription 3) deficiency: (i) autosomal dominant HIES; (ii) clinical features: skin and internal abscesses, recurrent pneumonias, candidiasis, eczema, pneumatoceles, coarse facial features, delayed shedding of primary teeth, joint hyperextensibility, scoliosis, osteopenia, NIH STAT 3 score >40; (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ TH17 responses, B-cell abnormalities, defects in tissue remodeling.

• Authors evaluated the clinical and immunologic features of patients with AD (n=14), DOCK8-HIES (n=6), STAT3-HIES (n=7), and healthy controls (n=14) → (i) overall, clinical allergy and SPT results complied with serum specific IgE results; (ii) total serum IgE levels were similarly increased in AD, DOCK8-HIES and STAT3-HIES patients; (iii) AD patients showed the highest specific serum IgE levels against aeroallergens; (iv) DOCK8-HIES patients showed the highest specific serum IgE levels against food allergens; (v) TH2-cell numbers and clinical allergies were significantly increased in DOCK8-HIES and AD patients compared to STAT3-HIES patients and controls; (vi) natural Treg-cell counts were significantly increased in AD patients compared to DOCK8-HIES, STAT3-HIES and control individuals; (vii) STAT3-HIES patients had decreased TH17-cell counts and allergic diseases; (viii) in STAT3-HIES patients, serum IgE correlated negatively to eosinophils and TH2-cell counts; (ix) in DOCK8-HIES patients, serum IgE correlated positively to eosinophils and TH2-cell counts.


• Eosinophilic esophagitis (EoE): (i) prevalence in the general population: ~1/2,000 subjects; (ii) incidence is rising; (iii) male to female ratio=3:1; (iv) impact: significant morbidity, ↓ QoL, high cost; (v) pathogenesis: genetic susceptibility, environmental insults to the esophageal epithelium (e.g. allergens, infections, irritants) → epithelial barrier dysfunction (e.g. ↓ expression of the cell adhesion protein DSG1), ↑ secretion of TSLP and IL-33 → ↑ allergen entry through the epithelium → immune reaction to food or respiratory allergens → infiltration of eosinophils into esophageal mucosa → chronic inflammatory infiltrate (eosinophils, mast cells, a special basophil population, TH2 cells, iNKT cells) → esophageal fibrosis, remodelling (e.g. transdifferentiation of epithelial cells to a myofibroblast phenotype) and dysfunction; (vi) common causal foods in children: milk, egg, soy, wheat, beef, chicken; (vii) common causal foods in adults: legumes, nuts, fruits, wheat, milk, soy, egg; (viii) frequent association (40-90%) with other atopic diseases (asthma, allergic rhinitis, food allergy, atopic dermatitis).

• Diagnosis of EoE: (i) clinical history: abdominal pain, vomiting, dysphagia, heartburn, cough, choking, food aversion; (ii) complications: food impaction, failure to thrive, esophageal perforation, mental affectation; (iii) esophageal endoscopy: edema, white exudative plaques, mucosal rings (‘trachealization’), strictures, linear furrows, mucosal tearing; (iv) esophageal
biopsy (positive result: ≥15 eosinophils per high-power field; other findings: superficial layering, microabscesses, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, lamina propria fibrosis); (v) allergy testing (skin prick test [SPT], serum specific IgE, atopy patch test [APT]) with food and respiratory allergens; (vi) food elimination-reintroduction trials; (vii) detection of eosinophil-mediated inflammation (e.g. cationic eosinophil granule proteins) by SPECT imaging.

• Treatment of EoE: (i) diet options: 6-food elimination diet (milk, egg, wheat, soy, fish/seafood, peanut/tree nuts), diet guided by allergy tests, aminoacid formula; (ii) topical corticosteroids: low bioavailability and low potential for systemic adverse effects but ↑ risk of local fungal infection; (iii) systemic corticosteroids: effective, severe side effects; (iv) biologic therapies targeting the eosinophil (e.g. anti-IL-5 mAb, anti-IL-5R mAb); (v) esophageal dilation: might provide short-term symptomatic relief, only used if dietary and medical therapy has failed.

• Efficacy of dietary therapies in EoE: (i) elemental diet (in both children and adults): ~90%; (ii) empiric 6-food elimination diet (SFED) (in both children and adults): ~70%; (iii) diet guided by skin testing (SPT and atopy patch test): ~75% in children, ~30% in adults.

• Authors compared the efficacy of food-specific serum IgE-targeted elimination diet (sIgE-ED) and SFED in 43 adults with EoE → (i) mean number of eliminated foods per patient was significantly lower in sIgE-ED (3.81) than in SFED (6); (ii) most commonly foods withdrawn by sIgE-ED: wheat (85%), nuts (73%), cow’s milk (61%); (iii) sIgE-ED was effective, comparable to SFED in terms of clinical and histological remission; (iv) causative foods identified by food challenge: cow’s milk (64%), wheat (28%), egg (21%), legumes (7%); (v) serum specific IgE was more accurate than SPT and APT to detect offending foods (sensitivity 87.5%, specificity 68%), especially for cow’s milk.


• Anaphylaxis: (i) definition: acute life-threatening systemic hypersensitivity reaction; (ii) lifetime prevalence: 0.05-2%; (iii) mechanisms: release of mediators from mast cells and basophils (IgE-mediated, IgG-mediated, complement mediated, idiopathic); (iv) most common culprits: foods, drugs, hymenoptera venom, latex; (v) augmentation factors: exercise, alcohol, infections, NSAIDs, drugs, menses, stress; (vi) diagnosis: clinical history (NIAID/FAAN criteria: sensitivity=96.7%, specificity=82.4%), measurement of allergy mediators (e.g. serum tryptase, serum/urinary histamine or metabolites, serum PAF), allergy testing (e.g. sIgE detection by skin and in vitro tests); (vii) treatment in the acute setting: epinephrine (1st line therapy), antihistamines, corticosteroids, β2-agonists, oxygen, intravenous fluids; (viii) long-term management: allergen avoidance, epinephrine autoinjectors, immunotherapy.

• Neuromuscular blocking agents (NMBAs): frequent causal agents of anaphylaxis in the general anesthesia setting.

• Authors analyzed 2022 reports of NMBArelated anaphylaxis in the French National Pharmacovigilance Database → (i) 1247 reactions were severe (grades 3 and 4); (ii) 84 reactions (4.1%) were fatal, despite guideline-based therapy; (iii) independent risk factors associated with a fatal outcome: male gender (female gender: OR=0.4), emergency setting
(OR=2.6), history of hypertension (OR=2.5) or other cardiovascular disease (OR=4.4), obesity (OR=2.4), ongoing beta-blocker treatment (OR=4.2).

• **REFRACTORY ASTHMA: MECHANISMS, TARGETS, AND THERAPY** (Trevor JL, Deshane JS. Allergy 2014; 69: 817–827):

  - Asthma: (i) definition: chronic inflammatory respiratory disease characterized by small airways inflammation, hyperresponsiveness, obstruction and remodeling; (ii) prevalence: ~300 million people worldwide; (iii) impact: significant morbidity, ↓ QoL, mortality risk (250,000 deaths/year worldwide), high costs; (iv) several endotypes and phenotypes (e.g. TH2/eosinophilic inflammation; TH17/neutrophilic inflammation); (v) conventional therapy: inhaled glucocorticoids (IGCs), β2-adrenergic receptor agonists, antileukotrienes.

  • A patient with uncontrolled asthma may have: (i) unawareness of disease severity; (ii) a physician who is undertreating; (iii) comorbidities (e.g. GERD, obesity, chronic rhinosinusitis, vocal cord dysfunction); (iv) low adherence to treatment; (v) treatment-resistant disease; (vi) an alternative diagnosis.

  • ~10% of asthma patients do not benefit with conventional therapy (refractory asthma) → it is important to develop new therapies based on asthma pathogenesis.

  • Pathogenesis of allergic asthma: (i) disruption of airway epithelial tight junctions and activation of epithelial cells by allergens (e.g. house dust mite proteases, fungal spores, pollen germination), pollutants (e.g. cigarette smoke) and virus (e.g. respiratory syncytial virus) in a genetically susceptible subject → (ii) entry of allergens through the disrupted epithelium or intact epithelial cells (transcytosis) → (iii) secretion of TSLP, IL-25 and IL-33 from activated epithelial cells → (iv) activation of type 2 innate lymphoid cells (ILCs) by TSLP, IL-25 and IL-33 → (v) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from type 2 ILCs → (vi) activation of dendritic cells (DCs) by cytokines (TSLP, IL-25, IL-33) and PRR-mediated signalling → (vii) maturation of DCs (expression of TH2-favoring costimulatory molecules [OX40L]; secretion of TH2-attracting cytokines [CCL17, CCL22]; presentation of allergen-derived peptides in MHC-II molecules) → (viii) attraction and differentiation of TH2 cells via antigen presentation, costimulatory molecules (OX40L, CD80/CD86) and cytokine signalling (IL-4) → (ix) secretion of TH2-cytokines (IL-3, IL-4, IL-5, IL-13) from TH2 lymphocytes → (x) IgE production from B cells; attraction and activation of effector allergy cells (mast cells, eosinophils, basophils); mucus secretion by epithelial cells → (xi) airway inflammation, epithelial injury, bronchoconstriction, air trapping, airway remodeling (goblet cell hyperplasia, thickening of the reticular basement membrane, subbasement fibrosis, smooth muscle hypertrophy/hyperplasia, angiogenesis).

  • Risk factors for refractory asthma: (i) genetic variants affecting epithelial barrier, innate immunity or adaptive immunity (variants that ↑ asthma risk in one environment may ↓ risk in another environment), (ii) comorbidities (e.g. nasosinusal disease, obesity, GERD), (iii) respiratory infections (e.g. Mycoplasma pneumoniae), (iv) pollutants (e.g. smoking, particulate matter), (v) sensitization to fungi (e.g. severe asthma with fungal sensitization), (vi) airway TH17/neutrophilic inflammation; (vii) multiple allergies; (viii) marked airway remodeling.

  • Therapies for refractory asthma: (i) small-particle ICSs and LABAs targeting small airways; (ii) once daily LABAs (e.g. vilanterol); (iii) inhaled long-acting anticholinergics (e.g. tiotropium); (iv) HDAC2 inducers: theophylline (↓ steroid resistance); (v) vit D (immunomodulatory effects); (vi) macrolides (antimicrobial and immunomodulatory action); (vii) antifungal therapy (in patients...
with fungal sensitization); (viii) CRTH2 antagonists (block PGD2 action on TH2 cells, eosinophils and mast cells); (ix) antagonists of chemokine receptors (e.g. CCR3, expressed largely on eosinophils); (x) inhibitors of kinases such as p38MAPK; (xi) biologic therapies; (xii) bronchial thermoplasty (not approved for children <12 yrs of age).

- **Biologic therapies for asthma:** (i) important for patients who do not respond to conventional therapy; (ii) may benefit specific asthma endotypes/phenotypes (e.g. lebrikizumab in patients with ↑ periostin/IL-13); (iii) ~30 drugs are currently in clinical trials and dozens in development; (iv) outcomes of most trials have been disappointing; (v) main problems: lack of efficacy, high cost, low accessibility, side effects.

- **Examples of biologic therapies for asthma:** (i) anti-IgE mAb: omalizumab (the only FDA-approved biologic to treat asthma), (ii) anti-IL-4Rα mAb: dupilumab (blocks IL-4 and IL-13 pathways), AMG-317; (iii) IL-4Rα antagonist: pitrakinra (blocks IL-4 and IL-13 pathways); (iv) IL-4 trapping agent: altrakincept; (v) anti-IL-5 mAb: mepolizumab, reslizumab; (vi) anti-IL-5R mAb: benralizumab (reduce eosinophil and basophil count); (vii) anti-IL-13 mAb: lebrikizumab, tralokinumab, anrurkinzumab; (viii) anti-TNF-α therapies: etanercept, infliximab, adalimumab, golimumab (risk of severe side effects); (ix) TLR7 agonists: imiquimod, resiquimod; (x) TLR9 agonist: QbG10; (xi) inhibitors of the TH17 pathway: anti-IL-17, anti-IL-23.

- **Mechanism of action of GCs:** diffusion across the cell membrane → binding to the glucocorticoid receptor α (GRα) in the cytoplasm → GRα liberates from chaperone proteins (hsp-90) → GRα enters the nucleus through nuclear import proteins (importin α) → GRα homodimerizes and binds to the promoter region of many genes (glucocorticoid response element) → the GC/GR complex switches off many activated inflammatory genes (cytokines, chemokines, adhesion molecules) and enhances anti-inflammatory genes.

- **Mechanisms of corticosteroid resistance:** (i) phosphorylation of the GRα by kinases (p38MAPK, JNK1), ↓ activity of phosphatases (MKP-1, PP2A) → ↓ nuclear translocation of GRα; (ii) ↑ expression of the isoform GC receptor beta (GRβ), which competes with activated GRα; (iii) ↑ proinflammatory transcription factors (NF-κB, AP-1, JNK); (iv) oxidative stress → activation of PI3Kδ → ↓ expression of histone deacetylase 2 (HDAC2), which normally switches off activated inflammatory genes; (v) polymorphisms of IL-10; (vi) vit D deficiency.

- **Strategies for managing GC resistance:** (i) anti-inflammatory drugs: phosphodiesterase 4 inhibitors (e.g. oral roflumilast for COPD), p38MAPK inhibitors, NF-κB inhibitors, macrolides; (ii) drugs that ↑ HDAC2 expression: theophylline, nortriptyline, PI3Kδ inhibitors; (iii) long-acting β2-receptor agonists (↑ PP2A, ↓ GRα phosphorylation, ↑ GRα translocation to the nucleus); (iv) antioxidants: Nrf2 activators; (v) vit D supplementation.

- **Asthma** is a complex clinical syndrome with multiple genotypes, endotypes and phenotypes → it is very unlikely that there is one “magic bullet” to cure all patients with asthma.

- **Futuristic approach in asthma/wheezing:** use of clinical data and biomarkers to identify specific asthma/wheezing phenotypes and endotypes → give individualized therapy (e.g. leukotriene-induced asthma → give antileukotrienes).

• Authors present a 20-page guideline about the definition, classification, diagnosis and treatment of urticaria.

• Definition of urticaria: sudden appearance of wheals ± angioedema. Typical features of a wheal: (i) central swelling of variable size, almost invariably surrounded by a reflex erythema; (ii) associated with itching or sometimes a burning sensation; (iii) duration usually between 1–24 hrs. Features of angioedema: (i) sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes; (ii) sometimes pain rather than itching; (iii) slower resolution that wheals (up to 72 hrs).

• It is very important to exclude other diseases with similar features: autoinflammatory diseases, urticarial vasculitis, hereditary angioedema, acquired angioedema, etc.

• Classification of urticaria: (i) spontaneous: acute (<6 wks) or chronic (>6 wks); (ii) inducible.

• Lifetime prevalence of urticaria: 1% of the population (chronic urticaria); 20% of the population (acute urticaria).

• Impact of chronic urticaria: significant morbidity, ↓ QoL (similar to angina pectoris; scores to measure QoL are useful), ↓ performance at school or work, high costs.

• Chronic spontaneous urticaria (CSU): (i) no clear triggers; (ii) 50% of cases have ‘autoimmune’ features [IgG1/IgG3 to FcεRIα or IgE; ↑ frequency of HLA DRB1*04]; (iii) coagulation, fibrinolysis and complement systems may have a role in pathogenesis; (iv) wheals usually last between 4 and 24 hrs; (v) concomitant angioedema may occur in ~50% of cases.

• Inducible urticaria: (i) triggered by stimuli such as cold, heat, touch, pressure, vibration, sunlight, water or exercise; (ii) wheals usually last <2 hrs after stimuli ceases, except for delayed pressure urticaria (similar to CSU wheals).

• Treatment of chronic urticaria: (i) 1st-line treatment: nonsedating anti-H1 at usual dosing (50% of patients may not respond); (ii) 2nd-line treatment: up to quadruple dose of anti-H1, such as desloratadine or levocetirizine (50% of patients may not respond → antihistamine-refractory CU); (iii) 3rd-line treatment: omalizumab, cyclosporin A (only FDA-approved immunosuppressant drug for CU), montelukast; (iv) other reported therapies: mast cell-stabilizing drugs (e.g. ketotifen), topical corticosteroids, systemic corticosteroids (3-10 days to control severe flares), biologic therapies (e.g. anti-TNF-α), intravenous immunoglobulin, epinephrine, desensitization, moisturizers, UV phototherapy, sulfasalazine, dapsone, colchicine, chloroquine, hydroxychloroquine, calcineurin inhibitors, mycophenolate, pseudoallergen-free diet, anticholinergics, androgens, selective serotonin reuptake inhibitors, tranexamic acid, psoralens, plasmapheresis, anticoagulants.

• Prognosis of chronic urticaria: 50% of cases may resolve within 1 yr; 75% of cases within 5 yrs.
ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY:

• **A CASE OF TRANSIENT ACQUIRED C1 INHIBITOR DEFICIENCY** (Melamed J, Ahuja-Malik A. Ann Allergy Asthma Immunol 2014; 113: 116-117):
  
  • C1 inhibitor (C1-INH): serine protease that ↓ complement and contact (kallikrein-kinin) systems.
  
  • Acquired angioedema with C1-INH deficiency (ACID): (i) recurrent episodes of bradykinin-mediated angioedema due to C1-INH consumption; (ii) pathophysiology: lymphoproliferative disorders, autoimmune diseases (e.g. SLE, Sjögren syndrome, vasculitis), monoclonal gammopathies → autoantibody production (including to C1-INH) → activation of the classical complement pathway → consumption of C1q, C1-INH and C4 → ↑ activity of FXII and kallikrein → ↑ bradykinin production → ACID; (iii) usually presents after 40 yrs of age; (iv) clinical manifestations: recurrent swelling of subcutaneous tissues (face, extremities, buttocks, genitals), abdominal organs (stomach, gut, bladder) or upper airways (larynx), unresponsive to antihistamines or corticosteroids.
  
  • Transient ACID: (i) rare entity; (ii) has been associated with HIV and parvovirus B17 infections in case reports; (iii) may be misdiagnosed as anaphylaxis.
  
  • Authors report the case of a 55-yr-old woman with a suspected isolated episode of transient ACID (massive angioedema of the right forearm; nausea, diarrhea, abdominal pain; hypotension; an erythematous, macular, patchy rash on the right flank and abdomen; ↓ C1-INH level, ↓ C4 level, ↓ activated partial thromboplastin time, ↑ D-dimer level) → previous clinical history: Lyme disease some months earlier, alcohol-induced hepatitis one month earlier, hypertension (lisinopril and amlodipine therapy for years) → successful treatment: intravenous fluids, methylprednisolone, piperacillin, diphenhydramine, famotidine → follow up some wks later: normal levels of complement proteins, no active infections detected.
  
  • Proposed contributing factors for transient ACID in this case: (i) vigorous IgM response to *Borrelia burgdorferi* (in antigen excess), with associated complement fixation and C1-INH consumption; (ii) treatment with lisinopril.
  
• **ALLERGIC CONTACT DERMATITIS** (Fonacier LS, Sher JM. Ann Allergy Asthma Immunol 2014; 113: 9-12):
  
  • Contact dermatitis: (i) definition: skin inflammation after direct contact with a substance; (ii) 2 main types: irritant contact dermatitis (most common form, direct irritation by substances, no immunologic sensitization), allergic contact dermatitis (ACD).
  
  • ACD: (i) type IV hypersensitivity reaction, (ii) skin inflammation usually occurs 8 to 48 hrs after contact with the allergen (can occur as early as 2 hrs and as late as 96 hrs), (iii) ACD and atopic dermatitis (AD) frequently coexist.
  
  • Risk factors for ACD: (i) AD (3-fold risk of contact dermatitis in hands); (ii) other skin barrier defects; (iii) repetitive contact with potential contact allergens.
  
  • Pathophysiology of ACD: (i) 1st exposure to a contact allergen → allergen entry through the skin → allergen processing by antigen-presenting cells (APCs) → allergen carrying by APCs to regional lymph nodes → allergen presentation to allergen-specific T cells → activation and
proliferation of allergen-specific T cells; (ii) subsequent exposures to the allergen → entry through the skin → activation of skin-homing memory T cells → inflammation → ACD.

- **Diagnosis of ACD:** (i) clinical history: history of AD, occupational history, hobbies, ACD lesions (time of onset, course, duration, triggers, response to treatment); (ii) examination of the lesions: distribution (high-yield locations: eyelids, face, lips, dorsal feet, upper back, proximal and lateral regions of the arms), morphology (acute lesions: pruritic, erythematous plaques and vesicles; chronic lesions: pink-red, dry, fissured and lichenified skin); (iii) patch testing: gold standard for diagnosis, standardized panels exist (e.g. the thin-layer rapid use epicutaneous test [T.R.U.E. Test]: FDA-approved, contains 35 antigens or mixes plus a negative control), all relevant allergens should be tested (e.g. fragrance mix-I and balsam of Peru [Myroxylon pereirae] only detect up to 70% of fragrance-allergic individuals; some rubber allergens are often missed with TRUE test), testing personal products can be useful (most important chemical classes: fragrances, preservatives, excipients, nickel, sun blocks).

- **Distribution of ACD lesions is the key to diagnosis** (e.g. ACD of periorbital areas and eyelids is commonly due to fragrances, the most common sensitizers in cosmetics).

- **Patch testing with nonstandardized antigens** (always review material safety): (i) agents applied to normal skin and left on (e.g. make-ups, moisturizers, lipsticks, sunscreens, perfumes, topical medications) should be tested “as is”; (ii) wash-off products (e.g. soap, shampoo, cream rinses) can be diluted to 1:100 or 1:10; (iii) only expert physicians should test household (e.g. detergents) and industrial products; (iv) recommended patch test concentration and vehicles can be found in [De Groot AC. Patch Testing: Test Concentrations and Vehicles for 4350 Chemicals. 3rd ed. Wapserveen, the Netherlands: Acdegroot Publishing; 2008].

- **Treatment:** (i) identification and avoidance of the culprit allergen (online databases of allergen-free products are useful; www.contactderm.org, www.AllergyFreeSkin.com), (ii) topical corticosteroids, (iii) topical emollients, (iv) systemic corticosteroids.

- **Systemic contact dermatitis (SCD):** (i) definition: acute dermatitis (e.g. baboon syndrome, dermatitis at sites of previous allergen exposure, dyshydrotic hand eczema) after a systemic exposure to a contact allergen; (ii) most common causes: metals (e.g. mercury, nickel, gold), drugs (e.g. aminoglycosides, corticosteroids, aminophylline), plants (e.g. the Compositae and Anacardiaceae plant families); (iii) food allergens can cause ACD and SCD (e.g. nickel, flavoring agents [balsam of Peru, oil of cinnamon, vanilla]); (iv) avoidance diets can be effective (e.g. foods to avoid in a balsam-restricted diet: citrus fruits, flavoring agents, spices [cinnamon, cloves, vanilla, curry, allspice, anise, ginger], spicy condiments, flavored tea and tobacco, chocolate, certain cough medicines, ice cream, spiced drinks, tomato-containing products).

- **CHANGING ROLES OF EOSINOPHILS IN HEALTH AND DISEASE** (Furuta GT, Atkins FD, Lee NA, Lee JJ. Ann Allergy Asthma Immunol 2014; 113: 3-8):

- **Dynamic history of eosinophils** (4 eras since Paul Erlich named them based on eosin staining): (i) Paul Erlich to the Mid-20th Century (1880-1960): eosinophils are innate defense cells (destruction of large nonphagocytizable parasites) and causal agents of allergic diseases and tissue damage; (ii) The Early Anti-inflammatory Years (1960-1980): eosinophils are recruited to inflamed tissues to ↓ the inflammatory activity of resident leukocytes (e.g. mastocytes); (iii) The “Gleich Era” (1980-2000): rebirth of the nonspecific and destructive nature of eosinophils contributing to host defense and diseases (enzymatic and cytotoxic activity of granule proteins);
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

(iv) The LIAR Hypothesis (2000-present): eosinophils contribute to tissue homeostasis through local immune and remodeling/repair activities (e.g. liver and skeletal muscle regeneration)

- **Eosinophil functions:** (i) proinflammatory: cytotoxicity, tissue damage, angiogenesis; (ii) antinflammatory: tissue repair and remodeling, immunomodulation.

- **Diseases with ↑ eosinophils:** (i) allergic diseases (atopic dermatitis, asthma, allergic rhinitis); (ii) hypereosinophilic syndrome; (iii) eosinophilic organ diseases; (iv) eosinophilic vasculitis (Churg-Strauss syndrome); (v) eosinophilic leukemia; (vi) other inflammatory processes.

- **Eosinophilic activity in disease:** (i) measurement methods: blood or tissue eosinophil counts, levels of eosinophil proteins in tissues or fluids; (ii) ↓ eosinophilic activity is usually associated with disease remission; (iii) to date, no eosinophil-related biomarker has proved sufficient utility as a surrogate of disease symptomatology, natural history, outcome or therapeutic success.

- **Specific therapies targeting the eosinophil:** (i) molecules: anti-IL-5 mAbs (mepolizumab, reslizumab), anti-IL-5Rα mAb (benralizumab, which also depletes basophils); (ii) variable efficacy in studies of patients with asthma, eosinophilic GI diseases, atopic dermatitis, Churg-Strauss syndrome and FIP1L1/PDGFRα-negative HES (outcomes appear to depend on the patient phenotype and/or primary end point examined); (iii) more research is necessary.

- **Additional therapeutic targets to ↓ eosinophils:** eotaxins, CCR3, CRTH2 (Chemoattractant Receptor-homologous molecule expressed on TH2 cells), TH2-associated cytokines.

- **Absence of eosinophils** in mice or humans → no significant deleterious effect on health (apparently).

- **OMALIZUMAB EFFECTIVELY PREVENTS RECURRENT REFRACTORY ANAPHYLAXIS IN A PATIENT WITH MONOCLONAL MAST CELL ACTIVATION SYNDROME** (Jagdis A, Vadas P. Ann Allergy Asthma Immunol 2014; 113: 115-116):

  - **Monoclonal mast cell activation syndrome (MMAS):** (i) 1st described in 2007; (ii) definition: clonal mast cell disorder characterized by recurrent symptoms of mast cell degranulation (urticaria, bronchospasm, abdominal symptoms, hypotension) in patients who do not fulfill criteria for systemic mastocytosis (SM); (iii) patients with MMAS meet only 1 or 2 of the minor criteria for SM and do not exhibit the clusters of bone marrow mast cells; (iv) unknown natural history (some patients eventually fulfill the 3 minor criteria for SM); (v) therapy: antihistamines, antileukotrienes, mast cell stabilizers, corticosteroids; (vi) disease control can be difficult.

  - **Omalizumab:** (i) recombinant humanized anti-IgE mAb → binds to free IgE → ↓ IgE binding to its receptors, ↓ expression of IgE receptors → ↓ IgE-mediated inflammation; (ii) FDA-approved for severe asthma and antihistamine-refractory CU; (iii) efficacy has also been reported in mast cell activation disorders, anaphylaxis, eosinophilic chronic rhinosinusitis and atopic dermatitis.

  - **Authors report the case of a 31-yr-old woman with recurrent unprovoked life-threatening anaphylaxis** (urticaria, swelling, cough, dyspnea, chest tightness, dysphonia, abdominal pain, vomiting, hypotension, syncope, marked ↑ of serum tryptase) → laboratory: normal CBC, minimal ↑ of baseline serum tryptase, IgE=68 IU/mL → bone marrow biopsy: mild ↑ of mast cells and eosinophils, one compact cluster of mast cells (not meeting major criterion for SM), occasional mast cells with spindled morphology, rare mast cells with weak anti-CD25 staining → cytogenetic analysis: Asp816Val c-KIT mutation → diagnosis: MMAS → unsuccessful
therapy: cetirizine (20 mg/d), ranitidine (150 mg bid), sodium cromoglycate (200 mg tid), montelukast (10 mg/d), ketotifen (4 mg bid), desloratadine (5 mg/d), hydroxychloroquine (200 mg/d) → partially successful therapy: omalizumab 300 mg SC every 4 wks continuously → follow-up at 11 months: 1 anaphylactic reaction requiring epinephrine, 2 milder reactions, no adverse effects of omalizumab, ↓ use of ketotifen (3 mg bid) and montelukast (suspended).

• Author’s commentaries: (i) 3rd reported case of omalizumab efficacy in MMAS (unclear mechanism of action); (ii) omalizumab may help patients with life-threatening refractory MMAS.


  • Penicillin (PNC): (i) discovered by Alexander Fleming from the fungus Penicillium; (ii) core structure: the β-lactam ring with the variable side chain R attached to the amide bridge to the ring carbon 6 atom; (iii) modifications at the R site → PNC-derivative antibiotics (e.g. the aminopenicillins amoxicillin and ampicillin contain an amine group in their side chain).

  • IgE-mediated PNC allergy: (i) self-reported in 5% of children and 10% of the population; (ii) confirmed in <1% of the population; (iii) incidence of anaphylaxis to PNCs=0.015-0.004% (fatality rate=0.002-0.0015%); (iv) major PNC allergen: benzylpenicilloyl determinant (95% of the PNC that is bound to proteins; commercially available as penicilloyl-polylysine [PPL]); (v) minor PNC allergens (minor determinant mixture, MDM): benzylpenicilloyloate, benzylpenilloate, benzylpenicilloyl-n-propylamine, PNC G; (vi) false-positive diagnosis of PNC allergy → unnecessary use of alternative antibiotics (e.g. quinolones, vancomycin, clindamycin, cephalosporins) that ↑ cost, bacterial resistance (e.g. methicillin-resistant S aureus, vancomycin-resistant enterococcus) and Clostridium difficile infection; (vii) reasons for false-positive diagnosis of PNC allergy: assumption that every rash during PNC therapy is caused by PNC allergy, wrong interpretation of skin or in vitro allergy tests; (viii) appropriate PNC skin testing and interpretation can ↓ the rate of false-positive diagnosis of PNC allergy.

  • Evaluation of a suspected IgE-mediated PNC allergy: (i) clinical history (often not reliable); (ii) in vitro testing (serum specific IgE, basophil activation testing); (iii) skin testing (reagents: PPL, benzylpenicilloyloate, benzylpenilloate, PNC G); (iv) drug challenge (up to 31% of patients require it to identify PNC allergy; it provides reassurance to subjects who might not be convinced by negative skin test results).

  • Commercial PPL, the major PNC antigenic determinant, is not widely available.

  • Authors evaluated 563 children with a history of PNC allergy → (i) skin testing only with PNC G had a good NPV (95.2% in all the sample; 82.4% in patients with a history of anaphylaxis); (ii) in patients with negative skin testing, a 3-dose graded challenge to the incriminated PNC was relatively safe → this approach can be useful when PPL is not available.

• THE DRY NEEDLE TECHNIQUE (Coop CA, Yip SK, Tankersley MS. Ann Allergy Asthma Immunol 2014; 113: 120-121):

  • Allergen immunotherapy (AIT): (i) only therapy that can change the natural history of IgE-mediated allergies (e.g. sublingual aeroallergen IT for 4-5 yrs generated sustained benefits for 7-12 yrs); (ii) method: administration of the specific allergen progressively to induce tolerance; (iii) widely used to treat asthma, allergic rhinitis and venom allergy; (iv) promising therapy for
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

- **atopic dermatitis** and **food allergy**; **(v) mechanisms:** ↑ Treg cells, ↑ specific IgG1 and IgG4, ↓ specific IgE, ↓ reactivity of mast cells and basophils; **(vi) most used modalities:** subcutaneous (SCIT), sublingual [it is unclear which modality has better outcomes]; **(vii) limitations:** allergic reactions (especially with SCIT), long treatment duration (≥3 yrs), insufficient efficacy (except for venom IT [≥90% efficacy]); **(viii) it is necessary to ↑ AIT efficacy, convenience and safety.**

- **Methods to prevent local and systemic reactions caused by AIT** (little evidence): **(i) premedication** with antihistamines, leukotriene antagonists or NSAIDs; **(ii) use of topical corticosteroids** over the injection site; **(iii) use of cold compresses** immediately after allergen injection; **(iv) mixing epinephrine with the allergen extract at the time of injection; (v) dose adjustments** for persistent large local reactions; **(vi) depression of the plunger** at a rate that does not result in wheal formation or excessive pain; **(vii) application of mild pressure** at the injection site for 1 min after needle removal to ↓ extract leakage; **(viii) the dry needle technique.**

- **Dry needle technique:** **(i) definition:** use of a separate needle to inject the allergen extract into the patient’s arm rather than using the needle from which the extract was drawn up into the syringe; **(ii) objective:** ↓ local reactions to immunotherapy; **(iii) non-evidence-based.**

- Authors surveyed 344 patients receiving SCIT (aeroallergen IT or venom IT) to assess their perceptions about the dry needle technique → **(i) most patients believed that the dry needle technique decreased or completely resolved their local reactions, systemic reactions and pain after injection; (ii) further research is needed.**

- **UNLOCKING THE STRESS-ALLERGY PUZZLE: NEED FOR A MORE COMPREHENSIVE STRESS MODEL** *(Wright RJ, Berin MC. Ann Allergy Asthma Immunol 2014; 113: 1-2):*

  - **Stress:** **(i) individual level:** fear, anxiety, depression; **(ii) family level:** family violence, family instability; **(iii) community level:** neighborhood violence, terrorism.

  - **Relation between stress and allergies:** **(i) allergic diseases → ↑ stress, ↓ QoL; (ii) stress → worsening of allergic diseases** (asthma, allergic rhinitis, atopic dermatitis, food allergy, anaphylaxis) and chronic urticaria; **(iii) stress → activation of coronary artery-associated mast cells → cardiac events.**

  - **Proposed pathogenic mechanisms of stress:** **(i) ↑ production of CRH (corticotropin-releasing hormone) → mast cell activation through CRHR-1, ↓ IL-10 secretion by Tregs; (ii) ↑ secretion of neuropeptides (substance P, neuropeptide Y) → ↑ expression of functional CRHR-1 on mast cells, mast cell degranulation through NTR (neurotensin receptor) and NK1R (neurokinin-1 receptor); (iii) dysfunctional HPA; (iv) ↓ cortisol production; (v) cortisol insensitivity; (vi) ↓ epithelial barrier function → ↑ allergen entry.**

  - Almost all leukocytes have receptors for hormones and neuropeptides released during stress (e.g. glucocorticoids, substance P, neuropeptide Y, CRH, prolactin, epinephrine, serotonin).

  - **Superior cervical ganglion neurons** can express Fc receptors for IgE and IgG, with calcium signaling after IgE-allergen crosslinking → nerves can be directly activated by allergen.

  - **Stress and anxiety:** therapeutic targets to improve management of patients with allergies.
**PEARLS IN ALLERGY AND IMMUNOLOGY: July 2014**


- Dedicator of cytokinesis 8 (*DOCK8*) gene encodes a guanine nucleotide exchange factor essential for the actin cytoskeleton functions (e.g. formation of the immunological synapse \(\rightarrow\) T-cell activation).

- *DOCK8* deficiency: (i) autosomal recessive hyper-IgE syndrome (HIES) with features of combined immunodeficiency; (ii) clinical features: severe viral infections (especially by HSV, VZV, HPV, molluscum contagiosum virus and JC viruses), fungal and bacterial infections, severe eczema, severe allergies, cancer susceptibility (e.g. squamous cell carcinoma, lymphoma); (iii) immune abnormalities: eosinophilia, ↑ IgE, ↓ T-cell migration, activation and function, ↓ T-cell and B-cell memory, ↓ CD8+ T-cell and NK-cell cytotoxicity, exhausted T-cell phenotype, impaired antibody production, impaired lymphoproliferation to antigens.

- Authors report the case of a patient with clinical and immunological parameters of HIES due to a partial *DOCK8* deficiency (milder clinical phenotype, no life-threatening infections, altered effector T-cell phenotype, impaired CD8+ T-cell and NK-cell cytotoxicity).


- Severe combined immunodeficiency (SCID): (i) definition: genetic defects causing marked ↓ in T-cell development and function \(\rightarrow\) lack of cellular and humoral immunity \(\rightarrow\) severe infections (including opportunistic), fatal course if not treated (HSCT, gene therapy, enzyme replacement therapy); (ii) newborns can be screened for SCID by measuring TRECs (T-cell receptor excision circles) in dried blood spot samples (DBSS) obtained from regular Guthrie cards.

- Agammaglobulinemia: (i) definition: genetic mutations that block B-cell maturation \(\rightarrow\) ↓ circulating B cells (<2% of peripheral blood lymphocytes) \(\rightarrow\) ↓ production of immunoglobulins \(\rightarrow\) severe infections; (ii) newborns can be screened for agammaglobulinemia by measuring KRECs (kappa-deleting recombination excision circles) in DBSS.

- Familial hemophagocytic lymphohistiocytosis (FHL): (i) often-fatal hyperinflammatory disorder caused by mutations in different genes; (ii) incidence: 1/50,000 live births; (iii) diagnosis: family history, clinical history, immune abnormalities (e.g. impaired lymphocyte cytotoxicity), genetic testing; (iv) acute treatment: immunosuppressive therapy, including chemotherapeutic agents; (v) curative treatment: HSCT; (vi) early diagnosis and treatment is life-saving \(\rightarrow\) FHL is a candidate for population-scale newborn screening (limitation: large diversity of mutations); (vii) in Sweden, ~50% of FHL cases are homozygous for an inversion straddling the *UNC13D* locus (candidate gene for newborn screening).

- Authors report a successful combined newborn screening assay for: (i) an *UNC13D* aberration endemic to Scandinavia; (ii) SCID (TRECs); (iii) agammaglobulinemia (KRECs).
• **Author’s commentary:** (i) merging disease screening markers in a single assay is likely to improve the cost-efficacy of newborn screening programs; (ii) genetic screening may be customized to indigenous genetic disease predisposition.

• **CURE OF HIV INFECTION: IS THE LONG WAIT OVER?** (Shearer WT. J Allergy Clin Immunol 2014; 134: 20-22):

  - This Journal issue has 2 reviews about progress in HIV-vaccine development and HIV-reservoir targeting.

  - **HIV: (i) impact:** fatal pandemic involving >35 million patients in the past 34 yrs; (ii) the 9 HIV genes have escaped carefully designed vaccines and antiviral therapy despite years of research and billions of dollars spent.

  - **Reasons for vaccine failure:** (i) HIV heterogeneity; (ii) high mutation rate of HIV peptides; (iii) inability of vaccine-induced antibodies to neutralize HIV.

  - **Strategies to improve HIV vaccines:** (i) building antigens that induce broad neutralizing HIV antibodies; (ii) targeting conserved viral sites (common to both original and variant viruses) and mosaics (multiple conserved sites); (iii) improving antibody affinity-maturation while preventing autoimmunity risk; (iv) improving generation of VIH-specific cytotoxic CD8+ T cells.

  - **Reason for failure of antiretroviral therapy:** survival of HIV virus in sanctuaries, principally resting CD4+ T lymphocytes (frequency=1 in a million cells; half-life=44 months).

  - **Strategies to improve HIV therapy:** (i) “shock and kill” approach to eradicate HIV from viral sanctuaries (combination of latency-reversing agents plus high-level ART); (ii) ↑ concentration of antiretroviral drugs in lymphatic tissue.

  - **Latency-reversing agents:** (i) histone deacetylase inhibitors (insufficient evidence), (ii) protein kinase agonists inducing NF-κB activation (prostratin, bryostatin).


  - **Dedicator of cytokinesis 8 (DOCK8) gene deficiency:** (i) autosomal recessive hyper-IgE syndrome with features of combined immunodeficiency; (ii) clinical features: sinopulmonary infections, skin and systemic viral infections, eczema, food allergy, cancer susceptibility; (iii) diagnosis: clinical history, immune abnormalities on laboratory testing, immunoblotting, gene sequencing (the 2 later are not widely available); (iv) the vast majority of patients lack DOCK8 expression and many have deletions in the DOCK8 gene; (v) DOCK8 deficiency can lead to early death from infection and malignancy → early diagnosis and treatment can be life-saving.

  - **Authors report a simple and robust flow cytometry assay for DOCK8 protein expression → advantages:** rapid (can be completed in hours), uses commercially available reagents and standard techniques, may also detect carriers; potential disadvantages: missense mutations or in-frame small deletions that do not affect protein expression may not be detected (minority of patients) → promising assay for diagnosis and post-transplant monitoring of DOCK8 deficiency.

- **STAT1**: transcription factor that mediate growth factor and cytokine signaling (e.g. interferon signaling). (i) Complete AR STAT1 deficiency → severe impairment of IFN-γ-mediated and IFN-α/β-mediated immunity → life-threatening intracellular bacterial, mycobacterial and viral diseases. (ii) Partial AR STAT1 deficiency → mild impairment of IFN-γ-mediated and IFN-α/β-mediated immunity → milder intracellular bacterial, mycobacterial and viral diseases; (iii) Dominant negative STAT1 mutations → impairment of IFN-γ-mediated immunity → susceptibility to mycobacterial diseases; (iv) AD gain-of-function (GOF) STAT1 mutations → ↓ production of TH17 cells → fungal infections, autoimmunity, esophageal carcinoma.

- **GOF STAT1 mutations**: ↑ response to interferons and IL-27, ↓ STAT3 function → TH17-cell deficiency, susceptibility to certain fungal (e.g. CMC) and bacterial infections, autoimmunity (e.g. hypothyroidism, autoimmune hepatitis, SLE, type I diabetes mellitus), malignancy (e.g. squamous cell cancers), arterial aneurysms. New reported phenotypes: IPEX-like syndrome; disseminated coccidioidomycosis, histoplasmosis and fusariosis; ↓ B-cell function.

- **Apophysomyces trapeziformis infection** has been related to penetrating trauma and diabetes.

- Authors report the case of a 24-yr-old man with disseminated mucormycosis (lymph nodes, muscle, heart, lungs and brain affection) caused by Apophysomyces trapeziformis → previous clinical history: no CMC, no conditions predisposing to mucormycosis → laboratory analysis: ↑ STAT1 phosphorylation, delay in STAT1 dephosphorylation, hyperresponsiveness to IFN-γ, ↓ IL-17-producing T cells → genetic analysis: novel heterozygous mutation c.1110G>C; p.E370D in the DNA-binding domain of STAT1 → successful acute treatment: liposomal amphotericin, micafungin, posaconazole, subcutaneous IFN-γ.

- Author’s commentaries: (i) 1st report of a primary immunodeficiency presenting as disseminated mucormycosis (STAT1 GOF mutations have not previously been associated with ↑ susceptibility to infections by filamentous molds); (ii) STAT1 GOF mutations can result in disseminated infections by Apophysomyces trapeziformis.


- **Nuclear factor kappa B (NF-κB)**: (i) essential transcription factor for host defense; (ii) in resting cells, inhibitory IxB proteins (IκBα, IκBβ, IκBε) sequester NF-κB complexes in the cytoplasm.

- **IκB kinase (IKK) complex**: (i) composition: 2 catalytically active kinases (IKKα, IKKβ), one regulatory subunit (IKKγ, also known as NF-κB essential modulator [NEMO]); (ii) function: phosphorylation and degradation of IκB proteins.
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

- **Canonical pathway of NF-κB activation**: several cell-activation signals → activation of the IKK complex → phosphorylation of IκBα by IKKβ → degradation of phosphorylated IκBα → liberation of NF-κB → translocation of NF-κB to the nucleus.

- **NEMO hypomorphic hemizygote mutations** (X-linked) and **IκBα hypermorphic mutations** (autosomal dominant) have been reported to cause immunodeficiency (susceptibility to severe bacterial, mycobacterial and viral infections), usually associated with **ectodermal dysplasia** (EDA).

- An autosomal-recessive mutation in IKKα has been associated with an in utero lethal Cocoon syndrome characterized by multiple fetal malformations.

- Authors report the case of a 18-month-old female born to 1st-degree consanguineous parents → positive family history: brother died at age 1 month from E coli sepsis and meningitis, 3 paternal grand uncles died in infancy with febrile illnesses → clinical manifestations: severe early-onset infections (omphalitis, delayed separation of the umbilical cord, disseminated BCGosis, Salmonella sepsis, infections by several microorganisms including Acinetobacter sp, Enterobacter sp, Stenotrophomonas sp, Achromobacter sp, rotavirus and Candida), signs of EDA (conical teeth) → laboratory: normal neutrophil counts, T-cell counts, NK-cell counts, T-cell repertoire, T-cell proliferation to PHA, expression of MHCII molecules, respiratory burst, integrin expression and monocyte/dendritic cell phenotype; ↓ IgG, ↓ IgA, ↑ IgM; ↓ memory B cells; severely impaired production of IFNγ, IL-17A, TNFα, IL-6 and IL-12; lack of IKKβ protein → genetic analysis (exome sequencing): homozygous nonsense mutation c.321C>A in the *IKBKB* gene encoding the IKKβ protein, leading to a premature stop codon p.Y107X (parents were heterozygous carriers) → clinical course: insufficient response to therapy, patient died at 25 months of age → HSCT should be considered in other patients with similar disease.

- **IKBKB** gene mutations may also present as SCID with agammaglobulinemia (recently reported abstract).


  - **Activated phosphoinositide 3-kinase δ syndrome (APDS)**: (i) novel autosomal-dominant primary immunodeficiency; (ii) etiology: heterozygous gain-of-function mutation in the *PIK3CD* gene encoding the p110δ protein, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ); (iii) the c.3061G>A mutation (E1021K) is a frequent one; (iv) clinical features: recurrent respiratory infections, bronchiectasis, progressive lymphopenia, ↑ T-cell apoptosis, ↓ T-cell cytokine production, immunoglobulin class switch recombination defect (↑ IgM, normal or ↓ IgG and IgA); (v) variable clinical presentation: from an isolated antibody deficiency (well controlled by IgG substitution) to a combined immunodeficiency requiring HSCT.

  - Authors screened 139 patients with an immunoglobulin class switch recombination defect for the c.3061G>A mutation in *PIK3CD* gene → (i) 8 patients with APDS were detected; (ii) 2 of them developed B-cell lymphomas.
• Author’s commentaries: (i) APDS must be considered in patients with an immunoglobulin class switch recombination defect; (ii) APDS patients might have ↑ risk of malignancies (hypothesis: ↓ T-cell–mediated immune surveillance, uncontrolled B-cell proliferation).

• Selective p110δ inhibitors: (i) molecules: IC87114 and GS81101 (CAL-101 or Idelalisib); (ii) effect: ↓ activity of the mutant p110δ in cells of APDS patients ex vivo; (iii) potential therapy for patients with APDS; (iv) GS81101 has been used in clinical trials to treat chronic lymphocytic leukemia (good safety profile).

  • GATA2 gene encodes a transcription factor that regulates stem cell homeostasis.
  • GATA2 mutations: (i) diverse clinical phenotypes: myelodysplastic syndrome/acute myeloid leukemia; multilineage cytopenias; ↓ monocyte, B-cell and NK-cell counts; recurrent infections, including opportunistic (bacterial, mycobacterial, viral); lymphedema; (ii) the same mutation can result in varied phenotypes (hypothesis: modifier genes, environment, epigenetic factors).
  • Authors report 2 patients with hypogammaglobulinemia and defective antibody responses associated with a GATA2 mutation (c.C1061T; T354M; dominant negative effect) detected by whole-exome sequencing (patient 1: recurrent sinopulmonary infections; patient 2: asymptomatic into mid-adulthood; both patients had multilineage cytopenias).
  • Author’s commentary: consider GATA2 mutations in patients with hypogammaglobulinemia, particularly in the setting of abnormal lymphocyte subsets and monocytopenia.

  • Advances in HIV-vaccine development: (i) discovery of novel HIV-envelope targets for protective antibodies, (ii) demonstration that CD8+ T cells can control HIV-1 infection, (iii) development of immunogens to overcome diversity of T-cell epitopes, (iv) defining pathways to develop broad-neutralizing antibodies.
  • A safe and effective HIV-1 vaccine is a global priority but still appears years away.

• RECENT DEVELOPMENTS IN THE SEARCH FOR A CURE FOR HIV-1 INFECTION: TARGETING THE LATENT RESERVOIR FOR HIV-1 (Siliciano JD, Siliciano RF. J Allergy Clin Immunol 2014; 134: 12-19):
  • Antiretroviral therapy can control HIV-1 infection but does not cure it → main problem: latent HIV-1 reservoir in resting CD4+ T cells.
  • Authors discuss several strategies to eradicate the latent HIV-1 reservoir and provide a cure for HIV-1 infection.
  • There have been reports of patients cured from HIV (e.g. an adult with HIV and acute myeloid leukemia was cured after transplantation with CCR5-deficient hematopoietic stem cells).

Common variable immunodeficiency (CVID): (i) heterogeneous group of immunodeficiencies (diverse etiology and clinical presentation; involve B- or T-cell defects; only 15% of cases have confirmed genetic defects); (ii) prevalence: up to 1:25,000 subjects; (iii) clinical features: defective antibody responses; susceptibility to infections, autoimmunity and neoplasms.

Gathmann et al studied retrospectively 2212 patients with CVID → (i) symptom onset was very early (<10 yrs of age) in >1/3rd of patients; (ii) male subjects with early-onset CVID were more prone to pneumonia and less prone to other complications; (iii) diagnostic delay was high especially in early-onset patients; (iv) diagnostic delay was strongly related to ↓ patient survival; (v) higher doses of immunoglobulin therapy were associated with ↓ serious bacterial infections.

Human rhinovirus (HRV): (i) frequently cause of asthma exacerbations in children; (ii) HRV-C species is associated with more severe attacks than HRV-A and HRV-B.

Asthma patients had higher antibody responses to HRV-A and HRV-B, but a less efficacious immune response to HRV-C.

Many patients with seasonal allergic rhinitis are sensitized to multiple pollens, including cross-reacting panallergens → correct prescription of allergen immunotherapy (AIT) is not easy.

In patients allergic to multiple pollens, component-resolved diagnosis (CRD) can refine the diagnosis made with extract-based SPT or IgE assays and the consequent AIT prescription.

Gene defects in the IFN-γ/IL-12 and NF-κB signaling pathways → primary immunodeficiencies in which mycobacterial susceptibility is a strong phenotypic feature.

Burns et al describe a patient with a novel homozygous loss-of-function mutation in the gene encoding the subunit β of IκB kinase (IKKβ) → severe infections by mycobacteria and other bacteria, conical teeth, abnormal immunologic studies.

IKKβ deficiency has also been reported in a patient with SCID.

Bone marrow transplantation should be considered in patients with complete IKKβ deficiency.

Sialic acid–binding immunoglobulin-like lectin 7 (Siglec-7): (i) novel inhibitory receptor on allergy effector cells (mast cells and basophils); (ii) therapeutic target for allergic diseases.

Chou et al report an autosomal dominant mutation in GATA2 causing hypogammaglobulinemia, defective antibody responses and abnormal B-cell phenotyping (↓ naive B cells, ↑ marginal zone–like B cells [skewed differentiation of transitional B cells toward marginal zone–like B cells?] in 2 patients (patient 1: recurrent sinopulmonary infections; patient 2: asymptomatic into mid-adulthood; both patients had multilineage cytopenias).

GATA2 deficiency can present with diverse phenotypes.
PEDIATRIC ALLERGY AND IMMUNOLOGY:

  - Infantile colic, constipation, gastroesophageal reflux (GER): (i) common in infants <6 months of age; (ii) usually mild and transient at this age; (iii) cow’s milk (CM)-free diets are frequently prescribed, although pathogenic role of CM is debated (most evidence exists for constipation).
  - Wessel’s criteria for colic: crying/fussing >3 hrs/day, >3 days/wk for >3 consecutive wks.
  - Rome III criteria for constipation: <1 bowel movement every third day and/or crying/pain during defecation and/or palpable stool in left colic quadrant.
  - NASPGHAN/ESPGHAN criteria for GER: recurrent episodes of regurgitations and/or vomiting, irritability, hematemesis, wheezing or stridor in relation with GER.
  - Risk of avoidance diets: (i) malnutrition; (ii) ↓ QoL; (iii) ↑ medical costs; (iv) development of IgE-mediated allergy after food reintroduction.
  - Author’s commentaries: (i) CM allergy seems not to play a role in most young infants with transient colic, constipation or GER → restricting CM is not recommended; (ii) some infants with persistent and severe symptoms might need allergy testing and a diagnostic CM-free diet.
  - CM allergy (IgE- and non-IgE-mediated) rarely occurs through exclusive breastfeeding, except for allergic proctocolitis (benign non-IgE-mediated allergy characterized by isolated bloody stool during the 1st yr of life).

  - Food protein-induced enterocolitis syndrome (FPIES): (i) non-IgE-mediated allergy to food proteins; (ii) usually starts in the 1st yr of life (has also been described in adults); (iii) clinical history: vomiting, diarrhea, dehydration, hypotension, shock, acidemia, methemoglobinemia (2-6 hrs after eating the culprit food); (iv) frequent culprits: cow’s milk, soy, grains (potentially any food may trigger an FPIES reaction); (v) diagnosis: clinical history, OFC; (vi) differential diagnosis: sepsis, metabolic diseases; (vii) acute treatment: fluid resuscitation, parenteral corticosteroids; (viii) long-term treatment: allergen avoidance; (ix) prognosis: typically resolves by 3-5 yrs of age (OFCs are usually performed to confirm resolution).
  - Authors report the case of a 6-yr-old girl with an adverse reaction to amoxicillin (vomiting 1-2 h after ingesting AMX syrup, morbilliform rash the next day) → allergy testing: negative serum specific IgE to cefaclor, penicillin, ampicillin and AMX; negative SPT and intradermal tests to AMX and penicillin → open oral challenge with AMX: vomiting, diarrhoea, pallor, lethargy, hypotension, tachycardia, tachypnea, leukocytosis, neutrophilia, acidemia and methemoglobinemia starting 2 hrs after the 350 mg dose; successful treatment with intravenous fluids and hydrocortisone → final diagnosis: ‘drug-induced enterocolitis syndrome (DIES)’.
  - Author’s commentaries: (i) 1st report of DIES provoked by AMX (based on clinical history and drug challenge); (ii) enterocolitis syndrome can rarely be drug-induced.
• **GENERALIZED FIXED DRUG ERUPTION IN A CHILD DUE TO TRIMETHOPRIM/SULFAMETHOXAZOLE** (Can C, Akkelle E, Bay B, Arcan Ö, Yalcın Ö, Yazicioglu M. Pediatr Allergy Immunol 2014; 25: 413–415):

  - Fixed drug eruption (FDE): (i) common skin allergic reaction; (ii) pathogenic mechanism: type IVc CD8+ T-cell-mediated delayed hypersensitivity reaction; (iii) clinical features: recurrent red-brown round skin lesions appearing in the same location 30 min to 8 hrs after exposure to the culprit drug, usually a single lesion (multiple lesions can occur), frequent residual hyperpigmentation; (iv) most common affected sites: hands, lips, oral mucosa, genitalia; (v) >100 culprit drugs have been reported; (vi) most common culprit drugs: penicillins, sulfonamides, tetracyclines, pyrazolones, barbiturates, phenolphthalein; (vii) diagnosis: clinical history, skin biopsy, patch testing, drug challenge (gold standard).

  - Authors report the case of a 3-yr-old boy with generalized FDE after taking TMP/SMX (diagnostic features: characteristics of the skin lesions, relationship between drug intake and reaction onset, disease remission after drug withdrawal, histopathologic findings) → successful treatment: hydroxyzine, topical methylprednisolone aceponate → patch testing (~2 months after the reaction): doubtful reaction to TMP/SMX → drug challenge was not performed due to the risk of a more severe allergic reaction.


  - Vaccines: (i) one of the most cost-effective methods of all health interventions; (ii) ↓ morbidity and mortality of many infectious diseases (e.g. smallpox eradication); (iii) ~20 vaccines are currently in use; (iv) each year billions of doses are administered worldwide.

  - Adverse events to vaccines (3 to 83 per 100,000 doses of the most frequently used vaccines): (i) immediate allergy (minutes to hours): IgE-mediated (e.g. urticaria, angioedema, wheezing, GI symptoms, hypotension); (ii) delayed allergy (hours to days): usually non IgE-mediated (e.g. serum sickness, polyarthritis, erythema nodosum, maculopapular rash, delayed onset urticaria, erythema multiforme); (iii) non immunologic reactions (e.g. local reactions due to the injection itself or a foreign body; subcutaneous nodules after the injection of vaccines containing aluminum salts; nonspecific fever, irritability, drowsiness or rash; vasovagal reactions).

  - Local reactions: (i) can be treated with cool packs and analgesic drugs (these drugs may ↓ immune response to vaccination and should not be administered prophylactically); (ii) may be difficult to distinguish from infectious cellulitis (monitoring is recommended).

  - Importance of accurate diagnosis of vaccine allergy: (i) to prevent serious reactions; (ii) to avoid unnecessary vaccine restriction.

  - Hypersensitivity reactions to vaccines can be classified according to the extent (local, systemic), timing of the reaction (immediate, non-immediate) and severity (minor, moderate, major).

  - Immediate hypersensitivity to vaccines range from 1 per 50,000 doses for DTP to about 1 per 500,000–1,000,000 doses for most other vaccines.

  - Anaphylaxis to vaccines: (i) rare but possible (reported for nearly every vaccine); (ii) most often due to vaccine constituents (e.g. gelatin, egg, milk, chicken, preservatives, antibiotics, yeast, latex) rather than the microbial components; (iii) in many cases a specific culprit is not detected.
Important considerations regarding adverse reactions to vaccines: (i) confirm the adverse reaction (fever and local reactions are very common, generally self-limited, and usually do not contraindicate further doses); (ii) evaluate if the patient needs further doses of the culprit vaccine or similar vaccines (some patients mount adequate immune responses after fewer than the recommended vaccine doses; antibody measurements can be useful); (iii) if the clinical history and laboratory testing (e.g. serum tryptase) suggests an IgE-mediated reaction, perform in vivo and in vitro tests to detect specific IgE (sIgE) against the vaccine or its components (no single investigation alone is sufficiently predictive for vaccine allergy); (iv) patients with negative vaccine skin tests will usually tolerate the vaccine; (v) patients with positive vaccine skin tests might tolerate the vaccine (if benefits outweigh risk the vaccine should be administered gradually); (vi) it is prudent to observe the patient 30 min after vaccination; (vii) it is prudent to be prepared for anaphylaxis; (viii) if an IgE-mediated reaction to the vaccine is confirmed, try to detect the specific culprit allergen because other vaccines could contain the same allergen (e.g. a patient with gelatin allergy may react to MMR, varicella or influenza vaccines); (ix) in most cases, patients with suspected allergy to vaccines can receive subsequent vaccinations safely; (x) some vaccines might be more important than others (e.g. measles is a potential fatal disease; influenza infection is usually less life-threatening).

How to confirm an IgE-mediated allergy to a vaccine? (i) Suggestive clinical history: manifestations of mast cell degranulation within 4 hrs after immunization; (ii) specific IgE detection by skin testing (use the same vaccine brand that caused the reaction; falsely positive results may occur; “normal” delayed responses are common [most likely represent prior immunity]); SPT (usually with undiluted vaccine, consider using dilutions when there is a history of severe reaction), intradermal test with 1/100 diluted vaccine (nonirritating concentration).

How to confirm an IgE-mediated allergy to a vaccine component? (i) Suggestive clinical history: signs of mast cell degranulation within 4 hrs after exposure to a vaccine component (e.g. egg, gelatin, yeast, latex, chicken, antibiotics); (ii) specific IgE detection to the vaccine component: SPT, in vitro testing; (iii) allergen challenge.

Gelatin: (i) stabilizer (µg to mg quantities) of many vaccines (e.g. MMR, varicella, influenza, Japanese encephalitis, rabies); (ii) bovine or porcine origin (extensively cross-reactive; patients sensitized to pork or beef are at higher risk of gelatin allergy); (iii) most frequent culprit allergen in vaccines; (iv) strong association between gelatin allergy and HLA-DR9 (particularly prevalent in Japan); (v) common ingredient in processed foods, particularly candies and desserts.

How to diagnose gelatin allergy? (i) Clinical history: ask for reactions after gelatin ingestion, a negative history does not exclude gelatin allergy; (ii) sIgE detection in vitro; (iii) SPT with an office-made extract (not approved by the FDA): dissolve 1 teaspoon of sugared gelatin powder (any flavor) in 5 mL of normal saline (unsugared gelatin tends to gel at room temperature).

How to approach a patient with IgE-mediated gelatin allergy? Perform skin testing with gelatin-containing vaccines → (i) negative results → vaccinate the patient, observe 30 min afterward, be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

Egg protein (ovalbumin): (i) very low amounts in influenza, MMR and rabies vaccines (usually no risk for egg-allergic patients); (ii) higher amounts in yellow fever vaccine (be careful with egg-allergic patients).
The purpose of this summary is exclusively educational, to provide practical updated knowledge for Allergy/Immunology Physicians. It does not intend to replace the clinical criteria of the physician.

- **How to diagnose egg allergy?** (i) Clinical history: ask for reactions after egg ingestion; (ii) sIgE detection by skin and serum tests; (iii) oral food challenge.

- **How to approach a patient with IgE-mediated egg allergy who needs influenza vaccine?** (i) Administer an entire dose without previous skin tests, even in patients with anaphylaxis to egg (allergy tests are recommended in patients with a history of allergic reaction to the influenza vaccine itself); (ii) observe 30 min after vaccination; (iii) be prepared to manage anaphylaxis; (iv) injectable trivalent vaccine is preferred over nasal live attenuated vaccine because its safety in egg-allergic patients has been studied more extensively; (v) 2 egg-free influenza vaccines were recently approved for patients ≥18 yrs of age (Optaflu [Flucelvax] and Flublok).

- **How to approach a patient with IgE-mediated egg allergy who needs yellow fever vaccine?** Perform skin tests with the vaccine → (i) negative results → vaccinate the patient, observe 30 min afterward, be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

- **Yellow fever vaccine** may contain chicken proteins → follow the same approach (see last paragraph) when vaccinating chicken-allergic patients.

- **Yeast protein** (Saccharomyces cerevisiae; common baker’s or brewer’s yeast): (i) present in hepatitis B vaccines (up to 25 mg per dose) and quadrivalent human papillomavirus vaccine (<7 µg per dose); (ii) yeast allergy is rare.

- **How to diagnose yeast allergy?** (i) Clinical history: ask for reactions after yeast ingestion; (ii) sIgE detection by skin and serum tests to Saccharomyces cerevisiae.

- **How to approach a patient with IgE-mediated yeast allergy?** Perform skin testing with yeast-containing vaccines → (i) negative results → vaccinate the patient, observe 30 min afterward, be prepared for anaphylaxis; (ii) positive results → consider alternative approach to vaccination or vaccination in graded doses (take informed consent, be prepared for anaphylaxis).

- **Natural rubber latex:** (i) present in latex gloves and in the packaging of many vaccines (vial stopper, syringe plunger); (ii) risk of vaccine contamination with latex is very low → minimal risk of allergic reactions in patients with IgE-mediated latex allergy.

- **How to diagnose latex allergy?** (i) Clinical history: ask for immediate reactions after exposure to latex; (ii) sIgE detection by skin and serum tests.

- **How to approach a patient with IgE-mediated latex allergy?** (i) Use a vaccine without latex stopper; (ii) if not possible, remove the stopper and take the vaccine directly from the vial; (iii) if latex packaging cannot be avoided (eg. a prefilled syringe), vaccinate and observe the patient 30 min afterward, be prepared to treat anaphylaxis; (iv) do not use latex gloves.

- **Contact allergy to latex** → no contraindication for latex-containing vaccines.


- **Pertussis vaccines** (DTaP or Tdap) and **Sabin vaccine** may contain trace amounts of casein → be careful when vaccinating milk-allergic children (the vast majority of patients, even those with severe milk allergy, will tolerate these vaccines well).
• **Some vaccines** (e.g. polio, MMR, influenza) may contain traces of **antibiotics** (e.g. neomycin, gentamicin, streptomycin, polymyxin B) → be careful when vaccinating patients with **allergy to these compounds** (not including contact dermatitis).

• Vaccines commonly contain **aluminum** (adjuvant), which may cause **delayed-type allergic reactions** (including localized or generalized contact dermatitis and granulomatous reactions).

• Vaccines commonly contain **preservatives** (e.g. thimerosal, phenoxyethanol, formaldehyde), which may cause **delayed-type hypersensitivity reactions** (including contact dermatitis and generalized maculopapular rash).

• BCG, some MMR vaccines and some rotavirus vaccines contain **dextran**, which may cause **immediate reactions** (by complement-activating IgG antibodies?) and **delayed reactions** (e.g. maculopapular exanthema, erythema nodosum, urticarial vasculitis, neutrophilic dermatoses).

• Approaching a patient with nonsevere nonimmediate allergy to vaccine components: (i) patch tests can help to detect a specific culprit but they usually cannot predict the response to the vaccine; (ii) it is recommended to use **vaccines not containing the culprit agent** (if not possible, vaccination can usually be performed after evaluating risk vs benefit); (iii) **intramuscular administration of aluminum-containing vaccines** may prevent the formation of granulomas in aluminum-sensitized patients; (iv) **delayed urticarial reactions** often result from non-specific mast cell degranulation and do not contraindicate revaccination (premedication with antihistamines from 48 hrs before vaccination can be considered); (v) a previous **Arthus reaction** is not an absolute contraindication for revaccination.


  • **Primary immunodeficiencies (PIDs):** (i) inherited disorders of the immune system; (ii) prevalence: 1:10,000 subjects; (iii) impact: severe complications (infections, autoimmunity, neoplasms), ↑ mortality, ↓ QoL, high costs; (iv) **early diagnosis and treatment** can be lifesaving; (v) genetic diagnosis is usually important for therapy, prognosis and genetic counseling; (vi) when indicated, **definite therapy of severe PIDs** (e.g. HSCT) should not be delayed while waiting for genetic diagnosis.

  • **Severe combined immunodeficiency (SCID):** genetic defects causing **complete lack of T-cell development** (± other cell lineages) → lack of cellular and humoral immunity → severe infections (including opportunistic), fatal course if not treated (HSCT, gene therapy, enzyme replacement therapy).

  • **Combined immunodeficiency:** genetic defects causing **reduced T-cell function** → ↓ cellular and humoral immunity → severe infections (including opportunistic), immune dysregulation, usually fatal course if not treated (HSCT, gene therapy, enzyme replacement therapy).

Allergic rhinitis (AR): (i) definition: IgE-mediated inflammation of the nasal mucosa; (ii) prevalence: up to 40% of the population; (iii) impact: ↓ physical, psychological, economical and social well-being, ↓ school and work productivity, ↓ QoL, ↑ risk of asthma and comorbidities.

Authors performed a cross-sectional study in 1283 subjects (10–13 yrs old) to evaluate the relationships between allergic respiratory diseases and depressive/anxious mood using the partial directed acyclic graph → (i) AR increased the likelihood of depression; (ii) anxious condition and low socioeconomic status contributed to depressive mood.

Author’s commentary: treatment of AR can ↑ psychologic wellness and ↓ disease burden.


Severe allergic reactions to antituberculosis drugs represent a therapeutic challenge, especially in patients with multidrug-resistant infections [reasons: (i) patients require prompt therapy; (ii) patients need a combination of several drugs; (iii) therapy lasts months to years; (iv) in some cases it is difficult to find alternative drug regimens; (v) diagnostic tests are not standardized] → drug desensitization should be considered.

Author’s report a 10-yr-old boy with latent tuberculosis (positive PPD and QuantiFERON test), G6PD deficiency (risk of hemolysis to isoniazid) and hypersensitivity to rifampin and isoniazid (non-blistering urticarial skin rash responsive to antihistamines) → allergy testing: negative SPT to rifampin at 2 mg/ml, positive intradermal reaction (wheal=9 mm, flare=15 mm) to rifampin at 0.002 mg/ml (highest non-irritating concentration) → diagnosis: probable IgE-mediated rifampin hypersensitivity → successful treatment: 13-step, 390-min, oral desensitization to rifampin (maintenance dose was scheduled to 600 mg in the morning and 300 mg at night to prevent resensitization due to short rifampin half-life [3 hrs]).


Chronic granulomatous disease (CGD): (i) immunodeficiency caused by an inborn defect of the oxygen burst reaction; (ii) clinical features: severe bacterial and fungal infections, granuloma formation, inflammatory manifestations (e.g. colitis, interstitial pneumonitis, nodular pneumonia, neutrophilic dermatosis, granulomatous hepatitis, cystitis); (iii) high early mortality if untreated.

Forms of CGD: (i) X-linked CGD (the most frequent): mutations of the CYBB gene encoding for the gp91phox subunit of the NADPH oxidase complex; (ii) autosomal recessive CGD: mutations of the genes that encode for the p22phox, p47phox, p67phox, and p40phox subunits.

Treatment of CGD: (i) curative treatment: HSCT, gene therapy; (ii) supportive treatment to prevent infections: antibacterial prophylaxis (e.g. cotrimoxazole), antifungal prophylaxis (e.g. itraconazole), IFN-γ; (iii) supportive treatment for granulomas and inflammatory manifestations: immunosuppressive agents (corticosteroids, azathioprine, anti-TNF-α, thalidomide).

Itraconazole therapy: (i) reduces incidence of invasive aspergillosis; (ii) improves long-term outcomes in CGD patients; (iii) drug interactions must be considered (e.g. itraconazole raises levels of calcineurin inhibitors; rifampicin lowers itraconazole levels).
• **Acne vulgaris**: (i) common skin disease (~3–9% of the population); (ii) systemic isotretinoin is used for moderate-severe acne, usually for 3–6 months.

• Authors report the case of a 21-yr-old boy with X-linked CGD and acne vulgaris → systemic isotretinoin reduced blood itraconazole levels → Aspergillus disease was aggravated.

• **Author’s commentary**: (i) systemic isotretinoin treatment may reduce itraconazole levels, thus increasing the risk of fungal disease in CGD patients; (ii) hypothesis: systemic isotretinoin → induction of cytochrome P450 → ↑ itraconazole metabolism → ↓ itraconazole levels.


  • Hoyos-Bachiloglu et al.: ↑ latitude → ↓ sun exposure → ↓ vit D levels → ↑ IgE-mediated food-induced anaphylaxis.

  • Hovland V et al.: in adolescents with asthma, concomitant allergic rhinitis was associated with ↑ bronchial responsiveness and airways inflammation.

  • Abelius et al.: allergic children had ↑ Th2-like chemokine levels (CCL17, CCL18, CCL22), which were influenced by maternal chemokine levels.


  • **Vernal keratoconjunctivitis (VKC)**: (i) severe sight-threatening ocular allergy; (ii) more frequent in warm weather; (iii) usually starts <10 yrs of age; (iv) pathogenesis is not well understood; (v) clinical features: itching, redness, swelling, discharge, photophobia, giant papillae on the upper tarsal conjunctiva (cobbledstoning appearance), Horner-Trantas dots (eosinophil collections), corneal damage (ulcers, scars); (vi) therapy: conventional therapy for allergic conjunctivitis is usually insufficient, immunosuppressive therapy is generally required (topical corticosteroids, cyclosporine A, tacrolimus), surgery is reserved for complications.